REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments, the following remarks and the enclosed Rule 132 Declaration by Maria Caterina TURCO.

By this Amendment, claims 31-33, 35, 46-52 and 65-72 have been cancelled without prejudice or disclaimer.

Claims 30, 37, 38, 53 and 62-64 have been amended. The amendments are fully supported in the as-filed specification.

The claims presently pending herein are 30, 36-38, 53 and 62-64.

The rejections of claims 30, 37, 38, 53 and 62 under 35 U.S.C. § 112, second paragraph, have been remedied by inserting the definite article "A".

The objection to claim 31 under Rule 1.75(c) is rendered moot in view of its having been cancelled.

Claims 30, 32, 38, 50-53 and 63-72 have been rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness.

Claims 35-38, 47, 53 and 69-72 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

Claims 30-32, 46 and 62 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Reed et al. U.S. 6,696,558.

Claims 30-32, 46 and 62 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kohn et al. U.S. 5,652,223.

The foregoing rejections are respectfully traversed.

Claim 30 has been amended to recite monoclonal antibodies for specific epitopes corresponding to SEQ ID NOS:15, 16, 17 and 18.

The intended use has been limited to research and diagnostic use.

Claim 63 has been amended to represent the BAG-3 expression situation set forth in Tables 2 and 3 at page 27 and further confirmed by the observation in the Rule 132 Declaration, i.e., that BAG-3 overexpression is found in primary tumors.

Enablement and non-obviousness of the research and diagnostic use of the monoclonal antibody of the invention.

The rejection under 35 U.S.C. § 112, first paragraph, for failure to meet the enablement requirement is overcome by the submission herewith of a copy of the AC-1 hybridoma clone deposit receipt. (Deposit of Biological Material under the Budapest Treaty - mother clone.) This is referenced at page 20, line 10 of the specification.

The claimed invention is directed to the recognition by specific monoclonal antibodies of specific 15- or 16-mer epitopes corresponding to SEC ID NOS: 15, 16, 17 or 18, comprised within the BAG-3 protein (known at the time of filing the present application).

The selection of 4 (15- or 16-mer) epitopes out of a protein having a length of 575 amino acids as antigens for immunization and mice immunization have been clearly described in the present application, beginning at page 18, line 17 to page 19, line 27.

In brief, the monoclonal antibodies have been produced with 4 different peptides, each comprised in a multiple peptide construct called MAP-construct, comprising a N-terminal BAG-3 specific peptide (see the epitope defined by SEQ ID NO: 15).

Due to the Multiple Antigenic Peptide technique used for immunization, the monoclonal antibodies of the invention have been produced by a tetra-specific (four different specificities) hybridoma, obtained by immunization with a Multiple Antigen Peptide construct comprising 4 different epitopes as antigenic peptides. This allows "*to obtain particularly efficient antibodies*" i.e., antibodies able to detect "*proteins expressed in low amounts, as usually happens for many relevant proteins ... in primary cells*" (see page 18, lines 19-22).

The advantages of the present antibodies are that they allow the detection of the BAG-3 protein specifically, since all four immunizing peptides are specific for this BAG protein (as pointed out in the specification at page 18, lines 15-16), in primary cells where this protein is expressed at very low levels, and, as said above, in its native form.

By the use of Mab and the other reagents, the present application has disclosed preliminary, but clear evidence that BAG-3 modulation directly affects apoptosis in primary cells, and this has turned out to be particularly significant in tumors, where BAG-3 overexpression correlates with a lower apoptosis level and with a higher malignancy. This has been demonstrated in the Rule 132 Declaration, enclosure B, panel C, pictures a)-d) where the Mab of the invention is able to detect an increasing malignancy in thyroid specimens from the benign lesions, such as goiters, to the more malignant ones, such as anaplastic carcinomas. In the Declaration enclosure B, panel A, pictures a) and b) are controls, while panel B shows a schematic of the results obtained.

BAG-3 functions, as disclosed in the specification, have been achieved by using different BAG-3 specific reagents, such as antisense nucleotides, vectors overexpressing BAG-3 and the monoclonal antibodies claimed herein.

Evidence of this central role of BAG-3 has been obtained in both directions: i.e., either by overexpressing BAG-3 [with a pCDNA expression vector, see Tables 2 and 3 at page 27, in human 293 cells where overexpression protects cells from stress-induced apoptosis and in human osteosarcoma cells where overexpression inhibits apoptosis and allows the tumor to grow more than the control] or by down-modulating BAG-3, in a cell line (U937) and in primary cells, such as peripheral blood T-lymphocyte and monocytes, by BAG-3 antisense. In all these experiments, the invention's antibodies have been used to measure BAG-3 overexpression, after cell-permeabilization (see page 27, line 17), thus confirming their ability to recognize the antigen as expressed in a native form, a property which is useful for immunocytochemistry analysis.

Further data confirming Mab's use and their relevance in tumor diagnosis, have been reported in the Rule 132 Declaration, where immunocytochemistry data, with the Mab of the invention, show that BAG-3 is almost never detected in normal tissues, while

its expression increases to a detectable level in the more malignant forms of several tumors, such as lung, breast, prostate (immunohystochemistry picture in the Rule 132 Declaration, enclosure A) and ovarian cancer.

One of ordinary skill in the art would probably have been motivated to prepare monoclonal antibodies against this BAG protein, due to the lack of specific BAG-3 reagents before the present invention.

However, at the time of filing the present application, no specific motivation for preparing BAG-3 specific antibodies could be envisaged, as disclosed in the Reed reference where all of BAG-1, -2 and -3 were believed to share common cellular partners and the same *in vitro* function (see Reed, col. 19).

"*In summary, these results demonstrate that BAG-family proteins all contain a conserved BAG domain near their C-terminus that binds Hsc70/Hsp70, and that human BAG-family proteins can bind with high affinity to the ATPase domain of Hsc and inhibit its chaperone activity through a Hip-repressable mechanism.*"

At the time of filing the present application, however, one of ordinary skill in the art did not have any specific indication on how to produce BAG-3 Mabs, and if they would have shown the ability to detect the BAG-3 protein, expressed at a low level in primary cells, whether they would have any diagnostic value (see the Rule 132 Declaration).

These evidences were first disclosed in the present application and are confirmed by the enclosed Rule 132 Declaration.

As a matter of fact, the same wording used by the Examiner, reported from the Reed reference, highlights that those prior art antibodies "***may***" be produced, not that they "have been produced". Thus, ***monoclonal antibodies*** were actually ***not available at the time of filing of the present application***. This is confirmed also by the Applicant's comments on the prior art and in particular on the Reed Patent (WO00/14106 cited in the specification at page 4, line 19).

The advantages and the usefulness of the specific reagents prepared according to the present invention is supported by the experiments of the present invention, which have led to the discovery of the specific role of BAG-3 *in vivo* as a key apoptosis modulator and its implication in tumor growth. In the Rule 132 Declaration it is also shown that specificity for another member of this family (a BAG-1 antibody), did not show the same diagnostic relevance. Therefore, anti-BAG-3 Mab antibodies are peculiar in this sense.

By contrast, Reed's teaching is that the biological activity of BAG-3 is carried out by the C-terminal BAG common domain and is similar to one of the other BAG proteins.

The Examiner's rejection is based on the fact that Reed discloses peptide-specific anti-BAG antibodies and states, "*Such peptide antibodies may be raised against any BAG domain of any of the human BAG proteins*" (col. 11, lines 32-62 in Reed and on page 11 of the Examiner's Office Action) and that "SEQ ID NOS: 15-18 *are comprised within the BAG-3 sequence*", thus rendering the present antibodies obvious.

It is Applicants' position that the difference between a theoretical possibility, such as the one mentioned in Reed (and only in general terms) and an actual reagent, such as the claimed reagent prepared herein, is usually considered to be the "***cutting-edge difference***" between an invention which is enabled and satisfies the written description requirement (patentable) and an invention which is not (unpatentable).

Under the enablement and written description requirements, the information or guidance which is not present in the prior art, amounts to a gap that was filled only by the present invention, is that the monoclonal antibodies against SEQ ID NOS: 15-18 of the BAG-3, once produced, provides BAG-3 specific reagents useful as diagnostic and research reagents.

The Reed reference does not provide any specific suggestion in this direction.

The same holds true with respect to the disclosure of the Kohn reference, which only teaches that a protein with a BAG-3 amino acid sequence is the mediator of carboxyamido-triazole resistance. This is different from the actual role of BAG-3. The

Kohn reference also fails to teach how to obtain research and diagnostic reagents against BAG-3 epitopes.

Therefore, it is Applicants' opinion that the Examiner should apply the same level of written description and enablement requirements under 35 U.S.C. § 112, first paragraph, to the evaluation of the background art and to the present invention, i.e., being discriminating with regard to a purely hypothetical mention of monoclonal antibodies in the Kohn and Reed disclosures, ***where these reagents have not even been prepared*** (as confirmed by the lack of experimental examples in both disclosures (see, for example, in U.S. 5,652,223 Example 1: induction of CAI Resistant cells; Example 2: isolation of CAIR nucleotide sequence; Example 3: analysis of the CAIR protein sequence; Example 4: measure of CAIR expression in tissues by nucleic acid probing and Example 5: preparation of GST-CAIR-1 fusion protein for the interacting partners detection; no example teaches the preparation of specific monoclonal antibodies)) and the actual reagents of the present invention.

In fact, should a comparison with a prior art monoclonal antibody be necessary to further sustain the advantages and the non-obviousness of the claimed reagents, as also mentioned by the Examiner at page 13 of the Office Action, no real antibody availability could be observed in any of the cited references.

In order to demonstrate the obviousness of the present selection of epitopes for Mab production, the Examiner maintains that SEQ ID NOS: 15, 16, 17 and 18 are comprised within the Reed reference to SEQ ID NO: 6. It is Applicants' position that the issue is not the availability of the larger sequence, but whether the isolation of those epitopes for immunization purposes was suggested or not. ***And, in fact, it was not.*** Moreover, that selection by Applicants proved to yield particularly advantageous reagents.

Applicants also wish to address the Examiner's questions on the relationship between the MAP-construct (former claim 38), the hybridoma mother clone AC-1 (former claim 37) and the monospecific monoclonal antibodies produced by the

hybridoma (former claim 36), described in the present specification at page 18, lines 22-27 to page 19, lines 12-31.

Briefly, being that the immunization is carried out by using together the four (4) distinct MAP-constructs (each one comprising only one of the epitopes in a multiple spatial arrangement), the mother clone AC-1 obtained and deposited, secretes 4 different monoclonal antibodies with specificities against each specific eptiope, as confirmed by the ELISA assay shown in Table 4, page 30 and at page 20, lines 3-4.

All of these aspects are part of the claimed invention, with regard to monoclonal antibodies.

CONCLUSION

Based on the remarks above and also the results illustrated in the Rule 132 Declaration with regard to several tumors, BAG-3 expression appears to characterize their malignant state. Therefore, the PD02009 hybridoma secreting specific Mabs (AC-1) against epitopes SEQ ID NOS: 15, 16, 17 and 18 represent a very useful tool for BAG-3 detection, diagnostic purposes and tumor prognostic evaluation.

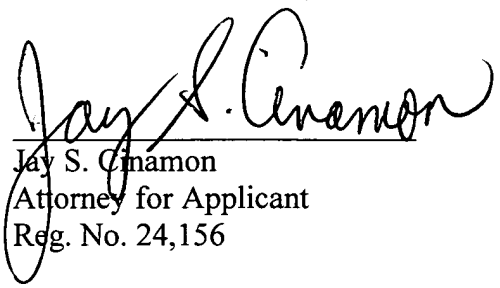
It is respectfully submitted that the rejections under U.S.C. §§ 112 and 103 have been overcome. The claims are deemed to distinguish over the teachings of Reed et al. and Kohn et al. Accordingly, withdrawal of the §§ 112 and 103 rejections are solicited.

The issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

ABELMAN, FRAYNE & SCHWAB
Attorneys for Applicant

By 
Jay S. Cinamon
Attorney for Applicant
Reg. No. 24,156

666 Third Avenue
New York, NY 10017-5621
Tel.: (212) 949-9022
Fax: (212) 949-9190